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Current Updates On The Role Of Apoptosis On Human Health And Disease

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Abstract:

Since the discovery of apoptosis, a plethora of other methods for cell death has been revealed. This study will look at the changes in caspase-dependent apoptosis that are linked to illness. More than 50 years of research on apoptosis signaling have shown that changes in these pathways are linked to human sickness. According to new research, apoptosis may be affected negatively or positively, leading to disease. Several therapeutic remedies are now in clinical studies or have previously been used in medical practice as a consequence of recent breakthroughs in the field of apoptosis control.

Keywords: apoptosis, cell death, health, cancer, diseases

Introduction

Since its earliest description, cell death, a basic biological process required for tissue development and control, has emerged as one with significant consequences in sickness. To maintain tissue homeostasis, mitosis must be kept in control by cell death. In either case, an increase or reduction in this process may lead to sickness. According to various morphological and biochemical criteria, several cell death processes have been found and categorized since the initial cell death description in the 1960s. In CDD, a slew of specialists in the area compiled a taxonomy of the many types. A review of caspase-dependent apoptosis and its impact on many human illnesses will be the focus of this paper(1-3). When caspase-dependent apoptosis is induced, a cell is destroyed in a regulated manner without cellular components spilling out or causing inflammation. For apoptosis to occur, a certain set of actions must take place that results in distinct morphological changes. Cellular components are condensed before the plasma membrane is blebbed, releasing tiny membrane-enclosed apoptotic entities that retain the cell components. Nearby cells or specially trained professional phagocytes quickly identify and destroy these infections without causing inflammation or injury to the tissue. Apoptosis and necrosis are characterized

by the biochemical and structural changes that occur when caspases are activated(4, 5). Before caspases may carry out their functions, they must be activated. More caspases are required to cleave the pro-domain for activation to be complete. Caspases may be divided into two categories: upstream caspases and downstream caspases. The cleavage and activation of upstream caspases are activated when additional enzyme molecules are brought together nearby, resulting in activation complexes. Once activated, they may activate downstream caspases and other enzyme-related molecules. Cleaving the pro-domain is the only way for upstream caspases to activate downstream caspases. Caspase activation and apoptosis are triggered by two distinct molecular processes: extrinsic and intrinsic(6-8).

Activation of particular trans-membrane receptors by ligands results in extrinsic apoptosis. Activation of the caspase cascade can only occur if all death receptors are linked to ligands and undergo conformational modifications. The Death Initiation Signaling Complex, a massive multi-protein complex, is formed as a consequence (DISC). Fas is activated by the death domain (DD) of a Fas-associated protein with an adaptor molecule (FASAP) when it comes into contact with its ligand (FADD). Cell death occurs as a result of FADD's Death Effector Domain (DED) binding and activating a homologous domain in caspase 8. When caspase 8 is active, additional caspase 8 molecules and downstream caspases like caspase 3 are activated. A variety of stressors, such as DNA damage and oxidative stress, activate the intrinsic pathway. Because of this, ATP synthesis is halted and caspase activation is triggered since the mitochondrial membrane potential is lost(9-11). All of these stressors work together to cause permeabilization of the mitochondrial membranes under all circumstances (MOMP). MOMP is the result of at least two metabolic processes that bring together various signals in the mitochondria (which are not mutually exclusive). Adenine Nucleotide Transporter (ANT) and Voltage-Dependent Anion Channel (VDAC) are required for the PTPC to open in the inner mitochondrial membrane, resulting in the pore-forming capabilities of numerous BCL-2 family members in the outer membrane (VDAC). When a protein has at least one Bcl-2 Homology (BH) domain, it is considered to be a member of the Bcl-2 family and an important regulator of this kind of cell death. They may be divided into anti-apoptotic and pro-apoptotic members based on whether they have three or four BH domains (Bcl-2, Bcl-xl, Bcl-w, Mcl-1), or two or three BH domains (Bak, Bak, Bcl-xs, Bok) (such as Bad, Bik, Bid, Bim, Noxa, Puma). Both pro-and anti-apoptotic members of the family may cause cell death by breaking membrane integrity, whereas anti-apoptotic members can prevent cell death by blocking the accumulation of pro-apoptotic members. Allosteric activation or induction of BHK3-only proteins in the mitochondria causes them to bind the pro-survival or antiapoptotic members of the family, eliminating or increasing their aggregated states(12, 13). When MOMP is active, several proteins, including Cytochrome C (CYTC), the apoptosis- inducing factor (AIF), endonuclease G (endo G), and the low-PI Direct IAP-binding protein, are released (DIABLO, also known as SMAC). Caspase 9 is activated to aid in the formation of the apoptosome at this point. Apoptosomes activate and cleaved caspase 9, which in turn activates caspase 3 and more molecules of caspase 9. A family of proteins called IAPS (Inhibitors of Apoptosis) exists in the cytoplasm because of the system's lethality and attaches to and inactivates caspases. The release of apoptosis- inducing proteins such as DIABLO/SMAC is also caused by MOMP. To activate the intrinsic pathway, Caspase 8 must first be activated through the mitochondrial route. Cleavage of the BH3-only protein BID by Caspases 8 may lead to the permeabilization of mitochondria and the onset of mitochondrial oxidative stress (MOMP)(14, 15) (Figure 1).

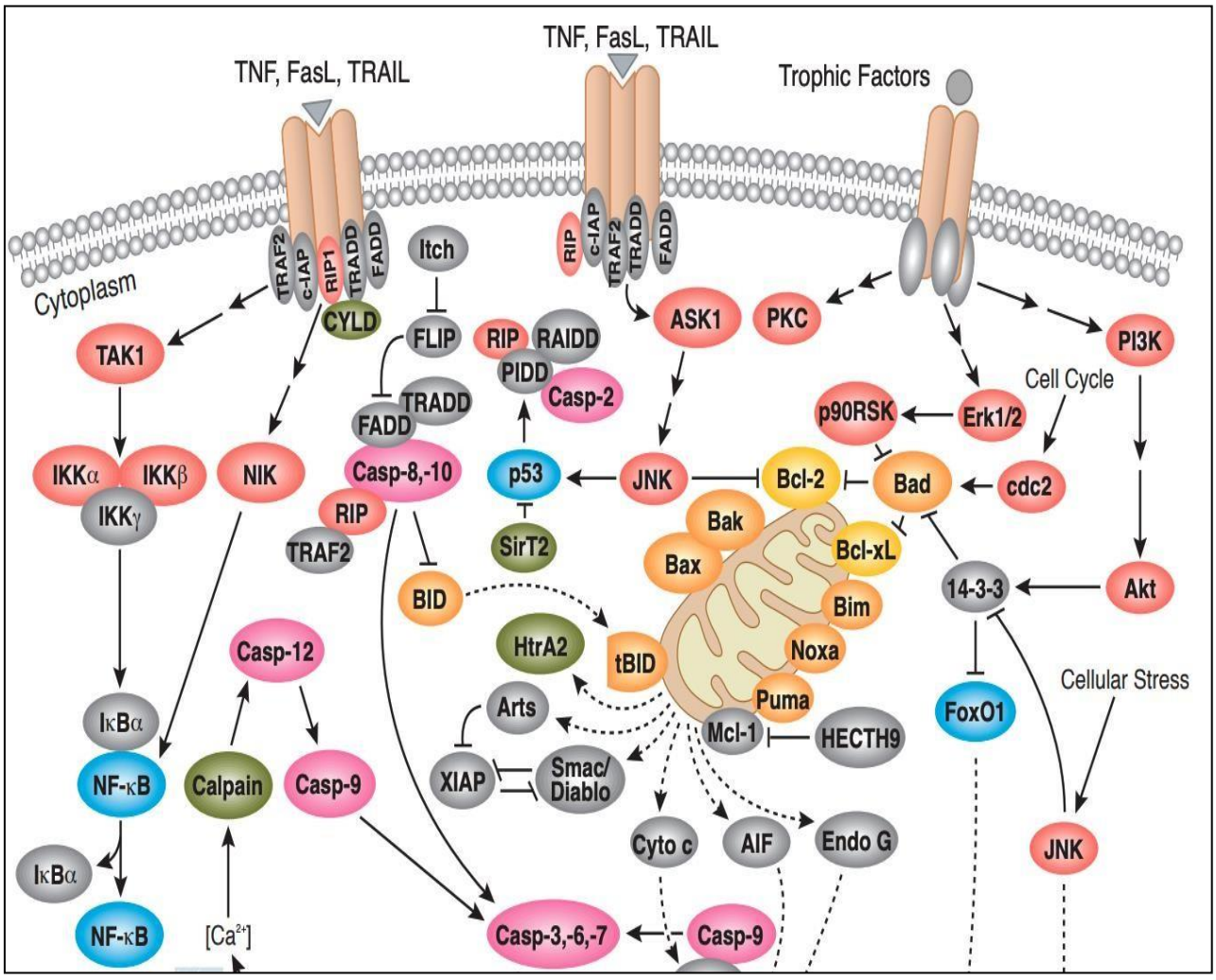

Figure 1: Apoptosis in Health and Disease

Cancer

It's not unexpected that apoptotic changes play a significant influence in cancer genesis given their importance in tissue homeostasis. Reactivating apoptotic pathways without blocking them is currently being investigated as a novel therapeutic strategy for treating treatment resistance caused by abnormalities in the system. The next sections provide a comprehensive list of proteins implicated in both intrinsic and extrinsic signaling pathways. Many stressors can trigger cell death, and the p53 gene is the most frequently altered in human cancers. Since cancer cells often alter upstream regulators of these pathways, this makes logical. These flaws are not explained in this review, which is a major flaw(16, 17).

Modifications to proteins in the BCL-2 family

When a subgroup of B-cell lymphomas was revealed to have Bcl-2, the protein was subsequently identified using this molecule. The Bcl-2 gene is over expressed in these tumors because of a common

translocation t. (14;18). For a long time, scientists suspected that this gene played an important role in the development of cancer. Alterations in Bcl-2 have been shown in several animal models since those early days to have a significant impact on the development of cancer. They are more susceptible to developing various forms of lymphoproliferative diseases in BCL-2 transgenic mice. It has been discovered that Bcl-2 is overexpressed in a wide range of cancers, including Hodgkin lymphoma, where it is associated with poor overall survival; breast cancer, where it is associated with aggressiveness of the tumor and decreased survival; and non-small and small cell lung carcinomas (in addition to the adenocarcinomas of the squamous type), as well as renal cell carcinomas. CLL patients with a new polymorphism in the BCL-2 promoter (938C>A) had a lower outcome and a more aggressive type of GBM, but women with breast or ovarian cancer fared better and lived longer(18, 19).

Many Bcl-2 family mutations have been discovered recently, suggesting that these proteins are becoming more and more important in the development of cancer. Mutations in the Bax and Bak genes have been discovered in cases of colon and stomach cancer. The lack of BAX/BAK suggests that these cells have compensation mechanisms in place since there is no increase in tumor formation when BAX/BAK is deficient. There are more tumors in Bax/pARF double-KO animals than normal mice, although this is not always a bad thing (sarcomas and carcinomas). When Bax is deleted in p53 mutant mice and SV40 big T antigen transgenic mice, tumor development is accelerated. CML and DLBCL, both of which are associated with mutations in the BH3 protein, are more common in animals lacking the bidding gene(20, 21).

Research into the Bcl-2 protein family has been going on for a long time, and the BH3-only proteins have attracted special attention in the creation of medications that imitate their ability to induce apoptosis in cancer cells. Phase I and II clinical studies are now underway for some of these. Patients with chronic lymphocytic leukemia are being tested with antisense oligonucleotides that target Bcl-2. These are now in phase III clinical studies.

Apoptosis malfunctions

P53 deficiency may be replaced by Apaf1 deficiency, which is often silenced or deactivated in human tumors. Apaf1 is down-regulated in melanoma, leukemia, glioblastoma, and cervical cancer through epigenetic processes. Apoptosome inhibitors have been hypothesized to exist in some malignancies with a faulty Cyt-C-dependent caspase 9 activation, but the underlying molecular mechanism is still a mystery." Another molecular reason for apoptosome failure has been revealed in Burkitt lymphoma cells: Apaf1 sequestration in lipid rafts(22, 23).

Dysfunction in the pathway of the death receptor

Oncology is greatly impacted by the modification of death receptor pathways, particularly in terms of tumor immunity. Cells may be protected from the immune system by decreasing the expression of death receptors; conversely, the expression of death ligands can be elevated to facilitate the destruction of reactive cells. In CD95 null mice, splenomegaly and lymphadenopathy are seen in a variety of human malignancies. There is a correlation between the depth of invasion and node metastasis and the presence of CD95, which is absent in most hepatocarcinoma and only found in less than 5 percent of

invading esophageal cancer cells found in 79% of patients. CD95 is also mutated in adult T cell leukemia and downregulated in various cancers such as colon, ovarian, cervical, endometrial, and melanoma (where lymphocyte infiltration of the invasive layer correlates with prognosis). As a result of Fas-L downr egulation and increased lymphocyte inflow, tumor volumes were reduced. This gene has been linked to cancers of the liver, breast, skin, and skeletal system; overexpression of FAS-L has been linked to more than 60% of these tumors" (reaching 95 percent in metastatic ones). It was also discovered in cancer patients' peripheral blood in the soluble (sFas-L) form, suggesting that Fas-L might be a potential immunosuppressive agent(24, 25).

CD95 signaling may be disrupted by other DISC mutations. These mutations and a complete deletion have been found in non-small-cell lung cancer and diffuse large B-cell lymphomas, respectively. It has also been shown that FADD deficiency has a pro-oncogenic effect owing to its unique role. Two examples of this include phosphorylated-FADD in lung cancers and FADD over expression in oral squamous cell carcinomas.

Several studies have shown that the Trail receptor pathway is critical in the development of tumors. Various animal models, including the emergence of spontaneous hematological malignancies in Trail KO mice, have indicated that Trail is a tumor suppressor. Tumor cells can avoid the immune system because of many defects, including CD95. Up to 20 percent of all human tumors, including breast cancer, head and neck cancer, and non-Hodgkin lymphomas, are known to have mutations in the trail receptors 1 and 2, which are located on chromosome 8p21-22(26, 27).

Cancer therapeutics based on death receptor activation was first limited by TNF and CD95 toxicity, although interest has grown since their discovery. Recombinant Trail's ability to cause cancer cells to die while sparing healthy cells has sparked a lot of interest in using this method to treat cancer. There has been a lot of investigation, but the cause of this strange behavior is still unknown.

Caspase activity is altered

Cancer cells might survive if caspases are inhibited since they are the last effectors of both intrinsic and extrinsic cell death. Mutations, promoter methylation, alternative splicing, or posttranslational modifications may be to blame for these aberrations. In other cases, mutant Caspases may behave as dominant negatives, preventing both the wild-type and defective proteins from activating.

An increase in the expression of cFLIPs, a protein that competes with caspase 8 for binding to FADD and so suppresses activation, in tumor cells may improve sensitivity to therapy, while a decrease in its expression may decrease sensitivity. IAPs play a significant role in the field of caspase inhibitors. A poor prognosis and therapeutic resistance have been linked to IAP changes in a range of human malignancies. As a result, a thorough assessment of the importance of IAP in a given cell setting is necessary since, in certain circumstances, IAP depletion corresponds with tumor formation. A wide range of processes, including the immunological response, mitosis, and apoptosis, have been revealed to be regulated by ionophore-activated protein (IAPs). These pathways are often altered in cancer, thus it's important to note that IAPs may influence carcinogenesis. The most significant IAP-regulated mechanism in cancer formation is NF-kB signaling. Inflammation, immunity, and cell viability are all controlled by XIAP, cIAP1,

and cIAP2. Additionally, cIAPs inhibit TNF from causing cell death. XIAP/survivin is a combination that stimulates cell motility kinases via activating the NF-kB pathway, according to recent research. Some research indicates that IAPs promote cell mobility, while others claim the polar opposite(28-30).

Smac/DIABLO and other IAP inhibitors have been created because of IAPs' role in cancer formation and capacity to regulate cell death, making them an attractive therapeutic target. There are some indications that they destroy cancer cells directly or at least render them more vulnerable to other killing agents while leaving normal cells unaffected. Several of these drugs are now being examined in clinical studies to discover whether they work(31, 32).

Disorders of the brain

For example, apoptosis is an important factor in the development of the central nervous system and is implicated in several adult brain illnesses, including neurodegenerative diseases and acute damage (i.e. stroke).

Diseases of the nervous system

Alzheimer's disease (AD). Amyloid-beta peptide buildup in extracellular and intracellular senile plaques and neurofibrillary tangles (NFTs) formed by hyperphosphorylated microtubule-associated protein tau are hallmarks of Alzheimer's disease (AD), a progressive neurodegenerative disease that causes neurons to die and leads to dementia. AD is also known as Alzheimer's disease, which is a kind of dementia. There is a significant link between the pathogenesis of Alzheimer's disease (AD) and neuronal death, and caspases seem to be involved in some of these processes. Caspase 3 activation and apoptosis were detected in cultured hippocampus neurons exposed to. In the cleavage of the amyloid precursor protein (APP), caspases 3 and 4 are considered to be the most important. C-terminal cleavage of tau by Caspase 3 may lead to tau hyperphosphorylation and an increase in NFTs. In addition, aberrant processing of tau protein is caused by -induced caspase 3 activation in Alzheimer's disease models. While in vivo, the caspase 6 enzyme degrades an N-terminal APP fragment, activating the death receptor 6 (DR6; also known as TNFRSF21), which leads to axonal degeneration(33-35).

An Alzheimer's disease (AD) model in which the anti-apoptotic gene Bcl-2 is overexpressed has been shown to reduce activation of caspase 9 and 3, therefore decreasing plaque and tangle development as well as improving memory and cognition.

Parkinson's disease (PD). As the second most prevalent chronic neurological condition, Parkinson's disease (PD) is characterized by problems with movement, such as tremors and rigidity. This results in the formation of fibrillar cytoplasmic inclusions called Lewy bodies. Abnormal stimulation of both internal and extrinsic apoptotic pathways may induce Parkinson's disease. Caspases 1 and 3 have been involved in apoptotic cell death in Parkinson's disease animal models. It has been shown that Parkinson's disease is associated with mutations in the parkin, DJ-1, and PTEN-IK1 genes (PINK1). The mitochondria-dependent apoptosis inhibitor PINK1 plays a role in this. Deficient PINK1 in humans and mice causes neurons to release cytochrome c earlier than in normal cells, leading to faster Bax translocation to mitochondria and cytochrome c release. There is an increase in caspase activity in the

absence of PIN1 (caspases 3 and 9). The extrinsic route has been demonstrated to be involved in the downregulation of PINK1 and other anti-apoptotic proteins, including Bcl-2, in Parkinson's disease patients. Researchers have found an increase in the expression of death receptors, such as FAS and TNFRSF10B, in neurons damaged by Parkinson's disease(36-38).

Huntington's disease (HD). Degeneration of medium spiny striatal and cortical neurons is the hallmark of Huntington's disease (HD). HTT gene mutations induce an aberrant extension of a trinucleotide CAG repeat in the protein's N-terminal polyglutamine tract, which results in a shortened polypeptide chain. HD is a hereditary condition. The formation of neuronal aggregates is thought to be a result of abnormal protein folding caused by an increase in polyglutamine. Caspases cleave mutant htt, and the accumulation of caspase-cleaved fragments in the brains of HD patients is early pathological discovery. Caspase 6 cleavage of mutant htt is essential for the development of behavioral and neuropathological symptoms in transgenic mice models. It is possible to use the activation of Caspases 6 in HD brains as an early marker of the disease, as it occurs before motor deficits(39, 40).

Caspase 8 is activated by another molecular mechanism that relies on the interacting protein 1 (HIP-1) and a polypeptide called Hippi (HIP-1 protein interactor). To help build the pro-apoptotic Hippi-Hip complex, there seems to be an increase in free cellular HIP-1 when ht (HD) is mutated (HD)(41, 42).

Inflammatory autoimmune diseases

Autoimmune illnesses are characterized by a decreased ability to tolerate self-antigens and the production of autoantibodies. Autoimmune diseases may be caused by both a lack of clearance of autoantigens and a lack of clearance of autoreactive cells; hence, apoptosis is crucial for maintaining immunological homeostasis and immune tolerance. Viral infections, gamma irradiation, and other stressful circumstances may all produce an increase in apoptosis, which in turn can lead to disease. Some researchers have proposed that the apoptotic and/or secondary necrotic processes that expose novel immunologically recognized epitopes in autoantigens and alter or delay their clearance, as well as prolonged exposure to apoptotic-inducing stimuli, cause an autoimmune response by cutting and altering autoantigens. IL-8, IL-1, TNF, and IFN- are all inflammatory cytokines that are produced as a consequence of immune complex development, and this leads to chronic inflammation and organ damage(43-46).

Defective cell apoptosis is linked to autoimmune illness. Lacking the Fas signaling pathway results in lymphadenopathy and splenomegaly, as well as a significant number of autoantibodies that mirror human systemic lupus (SLE). As a result of these results, the extrinsic apoptotic pathway and apoptosis may be used to regulate autoreactive T and B cells. Antibodies against the Fas signaling pathway in humans are responsible for the autoimmune lymphoproliferative syndrome (ALPS), which includes lymphoproliferation and autoimmunity in addition to a higher incidence of malignancies. These persons have 70% germline FAS mutations, whereas the remainder has somatic mutations in FAS ligand, caspase 10, or caspase 8. Almost all mutations have a dominant-negative effect on the function of the wild-type protein, limiting its ability to carry out its normal functions(47-50).

A growing body of evidence suggests that the intrinsic immune system route is just as important as its extrinsic counterpart and that any modifications to it might contribute to the emergence of autoimmune disorders. If you're interested in learning more about the effects of Bim KO mice on the immune system, you may want to check out this study on mice. Even while no mutations in the BH3-exclusive protein have been reported in individuals with autoimmune diseases, lower levels of Bim have been detected in a person with ALPS, and overexpression of pro-survival members of the bcl2 family has been documented in people with SLE(51-53).

As previously stated, autoimmune disorders are brought on by a lack of effective clearance of apoptotic cells. Autoantibodies produced by mice deficient in MGF-8 (a protein necessary for macrophage clearance of apoptotic cells) are identical to those seen in patients with SLE. Apoptotic cells release cellular debris that isn't removed by phagocytosis, leading to necrosis and subsequent discharge. These cellular antigens might set up an autoimmune reaction. SLE-like glomerulonephritis may also be seen in animals that lack the complement component C1q. The macrophages of at least half of SLE patients were shown to have decreased phagocytosis of apoptotic cells, as well as a lack of clearance of these cells(54-57).

Conclusion

Throughout the last half-century, cell death has been studied extensively and scientists have learned how it plays a role in a wide variety of illnesses. On the other hand, therapeutic use of this information is still in its infancy. The manipulation of various forms of cell death is expected to become more widespread in therapeutic practice in the coming years. Anti-tumor treatments, for example, face several challenges, including the activation of other death pathways after one has been inhibited by medication and the accidental death of "innocent bystanders" (i.e. healthy cells) during the process of killing diseased cells.

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